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## Review

# Extracranial stereotactic body radiotherapy. Review of main SBRT features and indications in primary tumors



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## ARTICLE INFO

## Article history:

Received 3 May 2013

Received in revised form

25 August 2013

Accepted 23 September 2013

## Keywords:

SBRT

Requirements

Organ motion

Early stage NCSLC

Hepatocellular carcinoma

Head and neck recurrences

## ABSTRACT

**Aim:** Review of main SBRT features and indications in primary tumors.

**Background:** Stereotactic body radiotherapy has been developed in the last few years. SBRT allows the hypofractionated treatment of extra cranial tumors, using either a single or limited number of dose fractions, and resulting in the delivery of a high biological effective dose with low toxicity.

**Material and methods:** SBRT requires a high level of accuracy for all phases of the treatment process: effective patient immobilization, precise target localization, highly conformed dosimetry and image guided systems for treatment verification. The implementation of SBRT in routine requires a careful considering of organ motion. Gating and tracking are effective ways to do so, and less invasive technologies “fiducials free” have been developed. Due to the hypofractionated scheme, the physician must pay attention to new dosimetric constraints in organ at risk and new radiobiological models are needed to assess the optimal fractionation and dose schemes.

**Results:** Currently, SBRT is safe and effective to treat primary tumors, which are otherwise untreatable with conventional radiotherapy or surgery. SBRT has quickly developed because of its excellent results in terms of tolerance and its high locoregional control rates. SBRT indications in primary tumors, such as lung primary tumors, have become a standard of care for inoperable patients. SBRT seems to be effective in many others indications in curative or palliative intent such as liver primary tumors, and novel indications and strategies are currently emerging in prostate cancer, head and neck tumor recurrences or pelvis reirradiations.

**Conclusion:** Currently, SBRT is mainly used when there is no other therapeutic alternative for the patient. This is due to the lack of randomized trials in these settings. However, the results shown in retrospective studies let us hope to impose SBRT as a new standard of care for many patients in the next few years.

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1507-1367/\$ – see front matter © 2013 Greater Poland Cancer Centre. Published by Elsevier Urban & Partner Sp. z o.o. All rights reserved.  
<http://dx.doi.org/10.1016/j.rpor.2013.09.009>

## 1. SBRT overview and requirements

Over the last decades stereotactic cranial radiosurgery has been successfully used for the treatment of intracranial lesions as it can precisely deliver a high dose of radiation to a tumor with very low dose to surrounding critical tissues. The good results obtained in intra-cranial localizations have led to the development of extra-cranial stereotactic radiation therapy known as stereotactic body radiation therapy (SBRT). SBRT, as a precise external beam radiation technique, allows the hypofractionated treatment of extra cranial tumors, using either a single or limited number of dose fractions, and resulting in the delivery of a high biological effective dose, often above 100 Gy which could be considered as “ablative” dose (stereotactic ablative body radiotherapy “SABR” is another suggested name for this technique). As in intracranial stereotactic radiosurgery, SBRT requires a high level of accuracy for all phases of the treatment process and organ and patient motion must be considered in the treatment planning. Recommendations and treatment quality control guidelines have also been established for SBRT.<sup>1,2</sup>

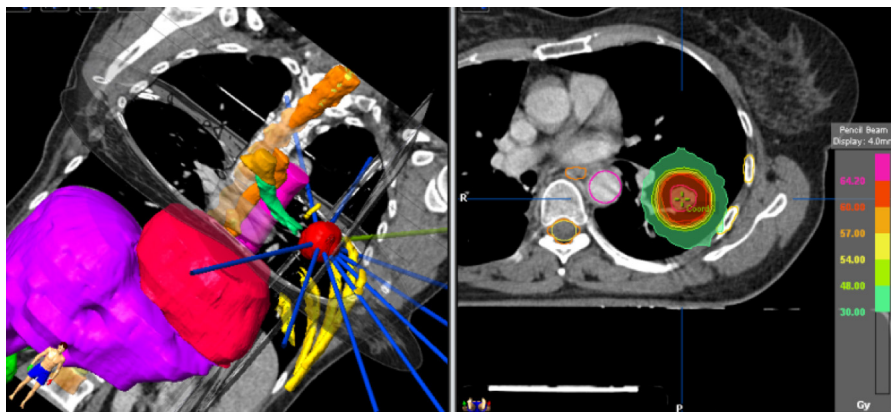
Accuracy in SBRT requires effective patient immobilization, precise target localization with the integration of modern image systems (CT, MRI, PET-CT) in order to properly define the tumor area for treatment and to further minimize radiation dose to healthy surrounding tissues; treatment planning also requires highly conformed dosimetry and isotropic dose fall-off (Fig. 1). Dose calculations should be carried out with algorithms which can account for the effects of tissue heterogeneities. Therefore, in order to deliver these accurate doses, linear accelerators must be equipped with micromultileaf collimators, the possibility of using multiple non overlapping beams of radiation and even intensity modulated radiation therapy.

One of the key challenges and requirements of SBRT is to reach the same “stereotactic accuracy” for extra cranial treatment as is achieved for cranial treatments. SBRT requires new image-guided verification techniques (IGRT), such as cone beam imaging or stereoscopic X-ray imaging, that allow a precise treatment of non-moving lesions (spine, prostate, etc.). For moving lesions such as lung and liver tumors, problems with accuracy still remain a challenge, and the assessment

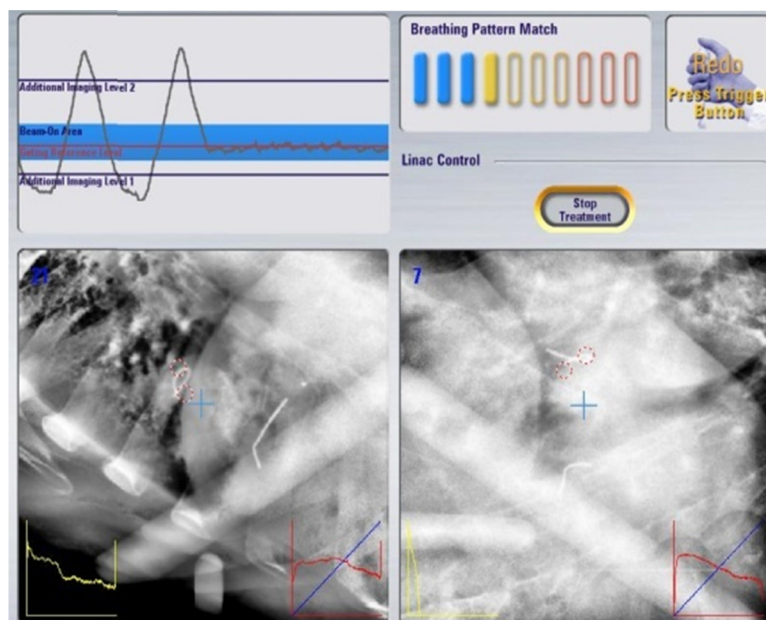
of tumor motion can be approached in different ways. Quantification of tumor motion can be measured and an ITV (internal target volume) can be deduced using a 4D-CT scan during the different respiratory phases. To reduce the target treatment area and spare healthy tissue more effectively, restrictive techniques, such as “dampening” with abdominal compression, can be used. Other methods called “compensating techniques” can not only quantify tumor motion but also have an intra-fraction control of tumor position and can treat the tumor exactly at the place where it is located, by visualizing its motion during the treatment. These techniques allow a precise delivery of high dose of radiation to the tumor with minimal dose to surrounding critical tissue (Fig. 1).

Novalis Exactrac Adaptive Gating® technique has been developed as a method that improves the accuracy of SBRT for lung and liver lesions, by monitoring organ tumor motion and irradiating within a selected area of the respiratory cycle. The tumor can be irradiated in this selected area by using internal markers previously implemented close to or directly into the tumor. Based on external markers, internal tumor motion is correlated with the external respiratory signal. During patient setup, infrared markers track the respiratory cycle. The Exactrac image guided system localizes the internal marker by X-rays and quantifies the tumor motion by correlating the external marker motion to the internal marker position. A selected area of this cycle is defined as the “beam on area” of irradiation. The validity of this model is verified in real time by Exactrac X-Rays<sup>3,4</sup> (Fig. 2).

“Tracking” is another compensating technique, and the tumor can be followed by “tracking” these fiducials or even by tracking certain tumors visible in the guidance X-ray image system. The CyberKnife system can track the tumor during the treatment using fiducials. However, transthoracic fiducials implantation under CT guidance can be responsible for pneumothorax (24–45%).<sup>5,6</sup> A fiducial-free tracking system, Xsight® Lung Tracking System (XLTS), has therefore been designed. This system requires that the tumor is wider than 15 mm and that it is visible in the orthogonal X-ray images (the tumor must be distant of at least 15 mm from any major vascular structures and its projection on the spine must be different from 45°). The system also uses a correlation model between external markers and the internal tumor positions to attain a millimetric precision. Both tracking systems can be combined



**Fig. 1 – SBRT treatment for early stage peripheral NSCL cancer. Highly conformed dosimetry with multiple beams. Dose prescribed: 60 Gy in 3 fractions of 20 Gy.**



**Fig. 2 – Organ motion compensating technique example: Novalis® Exactrac Adaptive Gating SBRT for lung and liver lesions. Monitoring organ tumor motion and irradiation within a selected area of the respiratory cycle with Exactrac image guide system localization of the internal marker.**

with the Synchrony Respiratory Tracking System in order to synchronize the beam targeting with the respiratory cycle.<sup>7</sup>

All these compensating techniques reduce the treated volume and the dose to the normal tissue. Therefore, accuracy in all phases of SBRT procedure is absolutely required in order to give effective and safe treatments with high and doses to the tumor and low risk of toxicity for the patient.

## 2. SBRT for primary lung tumors

Non small cell lung cancer (NSCLC) is a leading cause of cancer death in the world. Approximately 20% of patients are diagnosed with stage I, and surgery is the standard treatment for them with overall survival rates of 60–70%.<sup>8,9</sup> Surgical lobectomy may be associated with significant morbidity and mortality, and up to 25% of the patients cannot be operated due to a poor pulmonary function or comorbidities. With the wait and see policy, the overall median survival of these patients is only 9 months. Surgery is associated with the deterioration of quality of life, and in order to reduce its morbidity and risks of mortality, video-assisted thoracic surgery (VATS) has also been proposed.<sup>10,11</sup>

Until recently, for non operable stage I NSCLC, conventional radiotherapy (3D-CRT) has been the treatment of choice reaching local recurrence rates of 40% and specific survival of 39% at 3 years.<sup>12</sup>

Other alternatives, as radiofrequency ablation (RFA), have been explored for the treatment of patients who are not candidates for surgery on the basis of age, underlying lung disease, or other medical comorbidities. RFA works by transferring radiofrequency energy from a generator through an electrode, causing coagulation and necrosis of the tumor. The results of the published studies indicate the best results are achieved

in small lesions ( $\leq 3$  cm). Median survival of patients receiving RFA ranged from 8.6 months to 33 months, 1 year survival rate ranged from 63 to 85% and 3 year survival rate ranged from 15 to 46%. The 1–3 year local tumor progression-free rates were 45–83% and 25–57%, respectively. The adverse effects associated with RFA include pneumothorax (28–49%), pleural effusion, hemoptysis or pain.<sup>13,14</sup>

SBRT offers the possibility to treat these patients efficiently with a minimal risk of toxicity and to escalate dose of radiotherapy. SBRT has emerged as a new cancer therapy for the treatment of early-stage NSCLC, showing excellent clinical results without high costs in terms of toxicity, which has allowed to argue that the new technique is an alternative not only to surgery in inoperable patients, but perhaps also in operable patients.

The cost-effectiveness of these alternatives, 3D-CRT, SBRT, and RFA, has been analyzed. In comparison to 3D-CRT and RFA, SBRT was the most cost-effective treatment for medically inoperable NSCLC over a wide range of treatment and disease assumptions, so on these basis, SBRT could be the primary treatment approach for this disease.<sup>15</sup>

## 3. Lung SBRT retrospective studies

Early experience with SBRT for early stage NSCLC come from Sweden and Japan with excellent results in local control and survival in several retrospective studies.<sup>16–20</sup> Perhaps the most significant study was a multi-institutional Japanese study published by Onishi, including 245 patients, of whom 158 (65%) inoperable.<sup>21</sup> The dose administered was 18–75 Gy in 1–22 fractions with an average of biological equivalent dose (DEB) > 108 Gy. With a mean follow up of 24 months, the overall response rate was 85% and overall survival at 3 and

**Table 1 – Selected published series of stereotactic body radiotherapy for early stage NSCLC. Retrospective and phase I–II studies.**

Author	Patients	Study	Doses	Local control	Toxicity
Onishi 2004 <sup>21</sup>	245	Multicentric retrospective	18–75 Gy/1–22 fx	5 years 84%	7.6% grade $\geq$ 3
Baumann 2006 <sup>20</sup>	138	Multicentric retrospective	30–48 Gy/3 fx	33 months 88%	10% grade $\geq$ 3
McGarry 2005 <sup>22</sup>	47	Phase I	60–66 Gy/3 fx	15 months 79%	15% grade $\geq$ 3
Timmerman 2006 <sup>23,24</sup>	70	Phase II	60–66 Gy/3 fx	2 years 95%	20% grade $\geq$ 3
Zimmerman 2005 <sup>18</sup>	68	Retrospective	24–40 Gy/3–5 fx	3 years 88%	9% grade $\geq$ 3
Nyman 2006 <sup>19</sup>	57	Phase II	15 Gy/3 fx	3 years 92%	26% grade $\geq$ 3
Lagerwaard 2008 <sup>26</sup>	206	Multicentric retrospective	60 Gy (3 $\times$ 20 Gy/5 $\times$ 12 Gy/8 $\times$ 7.5 Gy)	3 years 93%	6% grade $\geq$ 3

5 years was 56% and 47%, respectively. This study showed that patients treated with SBRT with DEB > 100 Gy had better overall survival rates, and concluded that these doses are adequate to achieve good local control and survival in stage I NSCL.

#### 4. Lung SBRT prospective studies

Indiana University is one of the first prospective studies of SBRT for early-stage NSCLC. It is a phase I study of 47 inoperable stage I (T1–T2) patients. The maximum tolerated dose was not reached for tumors smaller than 5 cm, reaching levels of 20–22 Gy dose  $\times$  3 (60–66 Gy).<sup>22</sup> Based on this study, Timmerman performed a phase II in 70 patients using a scheme of 3 fractions of 20 Gy for T1 and 3 of 22 Gy for T2 tumors.<sup>23</sup> With a median follow-up of 17.5 months, the rate of LC at 2 years was 95% and overall survival was 55%. Patients with central tumors had a complication rate significantly higher than patients with peripheral tumors, with grade 5 toxicity recorded in 6 patients. In the multivariate analysis, tumor size also significantly influenced the occurrence of grade 3–5 toxicity although it was not such a powerful predictor as tumor location (Table 1).

This phase II study was the basis of the RTOG 0236 phase II study performed in 59 biopsy-proven peripheral T1T2N0M0 tumors which were treated with 54 Gy in three fractions. Patients with tumors  $\leq$  2 cm from the proximal bronchial tree were excluded. In the 55 evaluable patients, at a median follow-up of 34 months, there were two grade four adverse events, the 3-year primary tumor control rate was 98%, and 3-year local control rate was 91%. The 3-year disease-free and overall survival rates were 48 and 56%, respectively.<sup>24</sup>

A phase I/II study (RTOG 0813, NCT00750269) evaluated escalating doses delivered in five fractions for centrally located tumors. The goal of that trial was to determine

whether a modified schedule may minimize toxicity for centrally located tumors. The starting dose was 50 Gy in five fractions (10 Gy per fraction) with escalation to 12 Gy per fraction for tumors located within the proximal bronchial tree.<sup>25</sup>

In 2008, the Dutch multi-center experience in lung SBRT was published, including a total of 206 patients who had inoperable early stage NSCLC or who refused surgery.<sup>26</sup> Only 31% of the patients had histological confirmation of malignancy. Both central and peripheral tumors were included, using a “risk adjusted” fractionation scheme according to size and tumor location. Three fractions of 20 Gy were used for small tumors, 5 fractions of 12 Gy for large tumors or those close to chest wall and 8 fractions of 7.5 Gy for central tumors. Two years’ results were a 93% LC, 64% OS and grade 3 late toxicity  $\leq$  6%. The update of this study with 676 patients treated between 2003 and 2011 found a median overall survival of 41 months (35–47 months) and a 5 year local control of 89%<sup>27</sup> (Table 1).

This data from literature has already shown that SBRT can be firmly established as a standard of care for early stage NSCLC inoperable patients, with very high local control and overall survival rates and relatively low morbidity.<sup>24–26</sup>

These excellent results in inoperable patients bring the challenge to show if SBRT can also be an alternative to surgical treatment in operable patients, although this question is yet to be answered.<sup>28</sup>

There are recent data of a prospective phase II trial (RTOG 0618) of SBRT for early stage non-small cell lung cancer in operable patients with peripheral T1–T3, N0, M0 tumors. The prescription dose was 54 Gy (3 fractions of 18 Gy). Of 26 evaluable patients, 16% had SBRT related grade 3 toxicity. Median follow-up was 25 months. 2-year primary tumor failure rate of 7.7%. 2-year estimates of PFS and OS are 65.4% and 84.4%.<sup>29,11</sup> There is at least another ongoing phase II trial (Japanese Clinical Oncology group 0403) of SBRT in operable patients.<sup>30</sup>

**Table 2 – Selected published series of stereotactic body radiotherapy for primary liver tumors. Retrospective and phase I–II studies.**

Author	Patients	Study	Doses	Local control	Toxicity
Blomgren 1998 <sup>16</sup>	11	Retrospective	30 Gy 2–5 fx	1 year 95%	10% grade $\geq$ 3HCC Child B
Mendez Romero 2006 <sup>41</sup>	8	Prospective	25–37.5 Gy/3–5 fx	1 year 75%	18% grade $\geq$ 3HCC Child B
Choi 2006 <sup>42</sup>	20	Prospective	50 Gy/5 fx	1 year 80%	No grade $\geq$ 3
Tse 2008 <sup>43</sup>	31	Prospective	36 Gy/6 fx	1 year 65%	16% grade $\geq$ 3HCC Child B
Cardenes 2008 <sup>44,45</sup>	17	Prospective	36–48 Gy/3fx Child A40 Gy/3 fx Child B	1 year 96%	18% grade $\geq$ 3HCC Child B
Dewas 2012 <sup>48</sup>	42	Retrospective	40–45 Gy/3 fx	2 years 90–5%	10% grade $\geq$ 3
Andolino 2011 <sup>46</sup>	60	Retrospective	42 Gy/3 fx (Child A)40 Gy/5 fx (Child B)	2 years 90%	No grade $\geq$ 3



The started prospective phase III studies (ROSEL and STARS) randomizing surgery with SBRT in operable stage IA NSCLC had difficulties recruiting patients and were closed.<sup>31,32</sup>

At this moment the only phase III study comparing SBRT and surgery is the ACOSOG Z4099-RTOG 1021 trial. This trial compares sublobar resection with or without brachytherapy (I 125 implant at the resection margin) in high risk stage IA-IB NSCLC.<sup>33</sup>

## 5. Lung SBRT with intrafraction control of tumor motion

Accuracy in the treatment of lung tumors with SBRT is one of the main issues, and compensating techniques with gating and tracking can add an advantage to this treatments in terms of toxicity. Early experience with Novalis Exactrac Adaptive Gating has been published for 34 patients.<sup>34</sup> Peripheral lung lesions were treated with 3 fractions of 15–20 Gy and central lung lesions with 5 fractions of 10 Gy. Internal markers were implanted in all the patients with a 26% rate of pneumothorax. Two year local control was 93.8%. Clinical tolerance was excellent, and no acute or late lung grade 3 was observed.

Bibault<sup>35</sup> reported 51 patients treated with SBRT with the XLTS without fiducials. The local control and overall survival rate were, respectively, 92% and 85.5% at 1 year and 86% and 79.4% at 2 years. These efficacy results are comparable with other published series using fiducials. Only 7 cases of grade 1 and one grade 2 radiation pneumonitis were reported and obviously there was no pneumothorax case. No rib fractures were observed but this study only included tumors distant of at least 15 from the ribs. Indeed, due to the hypofractionation scheme and the high dose per fraction in SBRT, the ribs must be considered as organs at risk. In the literature, rib fracture occurs approximately in 40% of patients treated with SBRT and most reported risk factors for rib fractures are chest wall/tumor distance, female gender and maximum dose to 8cc to chest wall.<sup>36</sup>

Although not the subject of this review, it is interesting to note that SBRT has also an important role to play in the treatment of patients with oligometastases. SBRT appears to be an effective and well tolerated local therapy for patients with limited metastatic disease within the lung or the liver. Prospective phase I/II studies refer to 2-year local control rates that reach 92–96%, with very low toxicity related after SBRT doses from 48 to 60 Gy in 3 fractions.<sup>37,38</sup> Providing equivalent local control to surgical resection, SBRT may also be an alternative to surgery in patients with oligometastatic disease.

## 6. SBRT for liver primary tumors

Primary liver cancer is the world's third most common cause of cancer death and hepatocellular carcinoma (HCC) accounts for 85–90% of them. Risk factors for HCC include hepatitis B or C, alcohol ingestion and any cause of cirrhosis.<sup>39</sup> This underlying liver disease and the fact that HCC tend to be multifocal or with vascular invasion, make many patients with liver tumors poor candidates for surgery, and only 30–40% of the patients can benefit from curative treatments. In selected

patients, with early stage, adequate liver function (Child–Pugh A), performance status of 0, single or 3 lesions < 3 cm, and no associated diseases, surgical resection can result in 5-year survival rates of 40–70% and liver transplantation can cure both, the cancer and the underlying liver.<sup>40</sup> In patients with associated disease, early stage HCC and lesions < 3 cm away from large vessels, radiofrequency ablation and alcohol injection are also used as an alternative to surgery.

Cure with preserved liver function is a treatment goal and liver function is an important component of treatment decisions. Historically, radiation therapy has had a limited role in the treatment of liver tumors because of the low tolerance of the liver to radiation. The major dose-limiting concern is the risk of radiation-induced liver disease (RILD), and progression of Child–Pugh class must be considered as an end point of toxicity for those patients. However, because the functional units of the liver parenchyma obey the parallel model of radiobiology, a high dose radiation can be focally administered if sufficient normal tissue can be spared, and with SBRT it is possible to treat safely small or moderated sized hepatic tumors.

For HCC SBRT some specific considerations must be taken into account: GTV target delineation has to rely on phase arterial contrast CT or MRI imaging, the risk of microscopic extension should contemplate CTV margins of at least 5 mm, and in order to minimize toxicity it is imperative to use tight margins in PTV, therefore ITV should be reduced with restrictive or compensating techniques. Dose prescription and dosimetric constraints must take into account patient's Child–Pugh class score, and lesions size.

Blomgren, in 1991, first used SBRT to treat liver malignancies and since then retrospective and prospective studies have demonstrated efficacy and safety with local control rates in the range of 70–90% at 1 year (Table 2). Because SBRT is relative new, prospective data are quite scarce.<sup>16</sup>

## 7. HHC SBRT prospective studies

The first prospective study came from Mendez-Romero in 2006 who treated 8 HCCs (37.5 Gy in 3 fractions of 12.5 Gy or 25 Gy in 5 fractions of 5 Gy), with 1-year LC of 75% and severe toxicity only in a Child–Pugh B patient.<sup>41</sup> Choi in 2006 treated 20 patients with HCCs (15 Child class A), with 50 Gy in 5 fractions of 10 Gy, no episodes of severe toxicity were reported, 1-year LC of 80% and overall survival (OS) of 70%.<sup>42</sup> Another phase I study from Canada (Tse 2008) treated 31 HCCs, with a median dose of 36 Gy (range 24–54 Gy), tumors were generally large and half of the patients had large-vessel thrombosis.<sup>43</sup> No patients developed grade 4/5 liver toxicity. One-year LC was 65% and OS of 48%. The University of Indiana conducted a prospective study in 17 patients with HCCs.<sup>44,45</sup> The dose was escalated in Child–Pugh A patients from 36 Gy in 3 fractions of 12 Gy to 48 Gy in 3 fractions of 16 Gy. Two Child–Pugh B patients developed grade 3 hepatic toxicity at 42 Gy in 3 fractions, so subsequently these patients were treated with 40 Gy in 5 fractions of 8 Gy. Only 12% of the patients with a Child–Pugh score ≤ 7 developed hematologic or hepatic dysfunction > grade I, whereas 4 of 8 patients with score ≥ 8 developed progressive liver failure.

## 8. HCC SBRT retrospective studies

There are also several retrospective studies of interest. Andolino, continuing with the study from the University of Indiana, treated 60 patients with HCCs (36 Child–Pugh A and 24 Child–Pugh B), with a 2-year LC of 90% and OS of 67%.<sup>46</sup> Size of the lesions (>6 cm) and previous liver function were limiting factors (Child–Pugh score  $\geq 8$ ) for toxicity, and those patients should only be considered for SBRT as a “bridge therapy” to transplant. SBRT as definitive therapy for those ineligible for transplant should include 1–3 lesions, maximum tumor diameter  $\leq 6$  cm, and a Child–Pugh A–B score  $\leq 7$ . Son also reported the experience with 36 HCC patients treated with 30–39 Gy in 3 fractions. 11% of the patients developed progressions of Child–Pugh class when V18 Gy of >800 ml.<sup>47</sup>

Lille experience in 2012 reported a high local control rate (89% 1-year LC) in 42 patients treated for an HCC and six for a cholangiocarcinoma.<sup>48</sup> To track the lesions, they implemented fiducials (2–6) around each lesion. A total dose of 40–45 Gy at the 80% isodose was delivered. Local control rates at one and 2 years were 89% and 81% for the HCC. Overall survival and local control rate for cholangiocarcinoma were 100% at 1 year. Toxicity consisted mainly of nausea, abdominal pain and asthenia and was correlated with the duration of treatment ( $p < 0.04$ ). 12 patients presented with grade 3 or 4 gastro-intestinal side effects. Half of them were gastrointestinal toxicities involving lesions which were close to the digestive structures. Prognostic factors associated with better local control were lesion size <50 mm ( $p = 0.019$ ), PTV volume <200cc ( $p = 0.014$ ) and a delivered dose  $\geq 45$  Gy. Until now, SBRT appears to be a safe way to treat liver tumors with little toxicity, if lesions at immediate proximity of digestive structures are excluded.<sup>49</sup>

For cholangiocarcinomas both intra and extrahepatic surgical resections have historically been considered the only curative option. However, only about one-third of patients present with resectable disease and for unresectable patients the prognosis is particularly dismal with a median survival of only 2–6 months. Single agent or combination chemotherapy and conventionally fractionated radiotherapy seems to be largely ineffective. Improved local control and survival rates have been observed with higher radiotherapy doses suggesting dose escalation strategies as a promising therapeutic approach. SBRT experience in the treatment of unresectable cholangiocarcinoma is limited. Twenty-seven patients with unresectable cholangiocarcinoma ( $n = 26$  Klatskin tumors and one intrahepatic cholangiocarcinoma (IHCC)) were treated with SBRT.<sup>50</sup> The dose schedule was 45 Gy in three fractions. The median progression-free survival and overall survival were 6.7 and 10.6 months, respectively. With a median follow-up of 5.4 years, 6 patients had severe duodenal/pyloric ulceration and 3 patients developed duodenal stenosis.

Early experience with Novalis Exactrac Adaptive Gating in 13 HCC and 9 cholangiocarcinoma is presented in this review and supports its accuracy, efficacy and excellent tolerance. 11 Child–Pugh A HCC patients were treated with 3 fractions of 15–16 Gy and 2 Child–Pugh B with 10 fraction of 5 Gy. No acute or late grade  $\geq 3$  was observed. With a medium follow up of 18 months, local control was 91.7%. In the follow up, 4 patients developed intrahepatic progression with new

lesions and 2 presented distant metastases. Nine patients with Cholangiocarcinomas were also treated with SBRT and with standard concurrent capecitabine as a neoadjuvant combined treatment. The total dose was 50 Gy in 10 fractions. Tolerance was excellent and only one patient developed grade II transaminitis. Of the 9 patients, 8 underwent surgery, one patient progressed with liver metastases. All surgical margins were tumor free. One year local control was 100% and median survival was 17.67 months.

SBRT offers a safe and effective alternative for early stage HCCs and should be considered for patients who are poor candidates for surgery or transplantation, patients with compromised liver function must be treated more cautiously, and randomized studies are warranted to compare the efficacy of SBRT with other treatment modalities.

## 9. SBRT in prostate cancer

Prostate cancer is the most frequent male cancer in developed countries and radical prostatectomy and radiotherapy are treatment approaches for most localized tumors. Radiotherapy dose-escalation studies have shown a significantly better outcome (5-year disease control probability >80%). Prostate cancer is characterized by an  $\alpha/\beta$  ratio = 1.4 Gy, lower than that of most tumors or even of the late-responding normal tissues surrounding the tumor: the rectum and the bladder ( $\alpha/\beta = 3$ –5 Gy).<sup>51</sup> Thus, large treatment fractions (hypofractionation) may increase the tumor cell killing effect while biologically protecting the surrounding late responding normal tissues. Preliminary results of two pilot studies on extreme hypofractionation SBRT (5 daily fractions of 6.7 and 7.25 Gy over 5 and 5–9 days, respectively) have been reported, 5-year biochemical disease control rates above 90%.<sup>52,53</sup> Therefore, there is a need to test the effect on tolerance and outcome of large fractions. A prospective multi-center phase II study in France has been coordinated by Lartigau. The aim was to demonstrate the feasibility of delivering a  $3 \times 6$  Gy boost after IMRT or 3D delivery of 46 Gy in intermediate risk tumors. Seventy-two patients were included in less than 2 years in 4 participating centers (3 CyberKnife and 1 Linac). No acute toxicity was recorded and feasibility was excellent. Six Centers in France will participate in the new upcoming phase III PACE trial on the role of exclusive SBRT compared to radical prostatectomy.

## 10. SBRT in reirradiation

Most SBRT indications that have previously been described concern patients who are not amenable to surgery. For head-and-neck or pelvic tumors that were first treated with radiation therapy, SBRT enables to consider reirradiation, which was otherwise clearly not an option.<sup>54</sup> Indeed, most of the recurrences occur in the previously irradiated field and it is impossible in traditional radiotherapy to deliver enough dose-intensity to control the disease. The surgery is often impossible due to the previous irradiation and the location of the recurrence.

## 11. Head and neck SBRT irradiation

Reirradiation is an alternative for patients who are not candidates for surgical salvage although has a significant challenge regarding toxicity.<sup>55</sup> Three-year survival rates of 13–22% have been reported with external beam RT alone.<sup>56</sup> Results from phase I/II trials have also demonstrated the benefit of reirradiation with concurrent chemotherapy over observation.<sup>57,58</sup> Emerging data also support the safety of conformal delivery techniques, like intensity modulated radiation therapy, with potentially less treatment-related toxicity and local control improvement.<sup>59,60</sup>

SBRT is an attractive treatment modality for HNC reirradiation. The primary benefits of SBRT relative to conventional re-irradiation are shorter treatment times and decreased toxicity, which are achieved without compromising clinical outcomes.<sup>61,62</sup>

Currently an on-going phase II trial in Lille is leaded for recurrent head and neck squamous cell carcinoma, and preliminary experience was already published.<sup>63</sup> Forty patients were treated between June 2007 and January 2010 for a median tumor size of 29 mm. A dose of 36 Gy was delivered in 6 fractions. 14 patients received a concurrent infusion of cetuximab. After 25.6 months of median follow-up, 15 patients experienced a complete response and overall objective response was 79.4%. 20 presented with disease progression but only 3 with local relapse. 4 patients experienced a grade 3 toxicity but no carotid blowout was observed. This was explained by the fact that tumors invading more than one third of the carotid were not treated. Median overall survival was 13.6 months which is a good result considering the poor prognostic of these patients.

SBRT boost technique can be also a highly efficacious dose escalation modality in terms of local control. However, high

late complications have been observed and should be indicated only in selective cases because large treatment volumes treated with very high fractional doses have been related with high risk of developing late toxicities.<sup>64</sup>

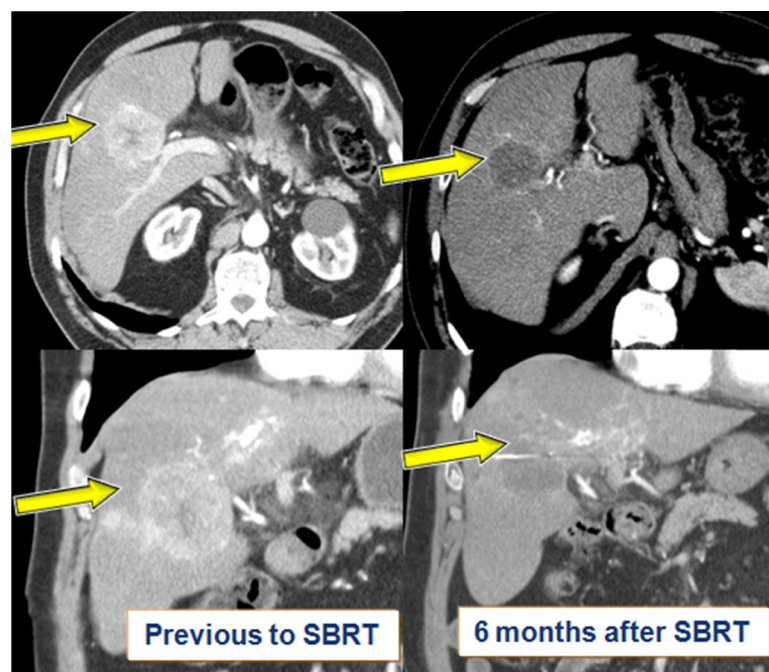
## 12. Pelvic SBRT reirradiation

Pelvic tumor recurrence is usually treated by surgery but in case of lateral pelvic invasion recurrence or proximity of the iliac vessel, local treatment cannot be achieved. Without treatment, local progression often causes pain and impacts the quality of life. Since June 2007, 16 patients with pelvic recurrence were reirradiated with the CyberKnife.<sup>65</sup> Primary tumors were rectal cancer (4 patients), anal canal (6 patients), uterine cervix cancer (4 patients), endometrial cancer (1 patient) and bladder carcinoma (1 patient). The prescribed dose was 36 Gy in 6 fractions. Of 8 patients, who had sciatic pain before treatment, 4 patients reported an improvement. The local control rate at 1 year was 51.4%. The treatment was well tolerated and we observed no grade 3 toxicity.

Reirradiation is often a complex situation in which there is no alternative and SBRT seems to be a safe and efficient option to treat tumor recurrences even if not in a curative intent. Nevertheless, further prospective studies are needed to precise the indications and the toxicity profile for these treatments.

## 13. Follow-up after SBRT

Dose distribution in SBRT is extremely different from conventional radiotherapy. Early and late reactions can also be very different. Radiologic aspect after SBRT can be sometimes very difficult to analyze. Indeed, RECIST criteria, which are



**Fig. 3 – Follow up with radiological evaluation of response after SBRT treatment for Hepatocellular carcinoma. Reduction of arterial contrast enhancement is included in the new RECIST criteria of response for HCC.**



based on the change of lesion size, appear to be inappropriate. After SBRT, lung condensation can mimic an increase of size of the lesion although there is no recurrence. Bibault<sup>66</sup> described the semiology that should lead to suspicion of recurrence: localization in continuation with treated lesion, pleural effusion, disappearance of initial bronchiectasis and morphological modifications of fibrosis contours. Timing of the appearance of these images is essential: early reactions occur between six and nine months late changes, after 12 months, including size or contours modifications with enlarging opacity can be considered high-risk CT changes and recurrent disease should be suspected if seen with SUVmax  $\geq 5$  on PET, with a high predictive value.<sup>67</sup>

The paradigms of evaluation of liver lesions have been modified in regard of radiologic aspect after novel targeted therapies. For example, modified RECIST criteria have been developed for HCC. Jarraya<sup>68</sup> showed that RECIST criteria could lead to a misinterpretation of some lesions, especially in case of tumors that become necrotic after treatment. They suggest using lobular enhancement, total necrosis and rimming enhancement in addition to RECIST criteria (Fig. 3). Metabolic imaging like FDG-PET could also be useful but has not been evaluated in this indication. If considered, FDG-PET imaging must not be realized before a minimal delay of 6 months. Indeed, initial inflammatory reactions caused by high doses per fraction/SBRT can be responsible for false-positive results; however, some publications suggest metabolic response after SBRT could be a good prognostic factor of loco-regional relapse.<sup>69</sup> Currently, the optimal supervision after SBRT is not known. Follow-up must be carried by radiologists who are accustomed to SBRT post-therapeutic aspects.

## 14. Conclusion

Stereotactic body radiation therapy is a recent radiotherapy technique, which has quickly developed because of its excellent results in terms of tolerance and its high loco-regional control rates. The implementation of SBRT in routine requires a careful considering of organ motion. Gating and Tracking are effective ways to do so, and the development of new technologies such as X-Sight Lung have made it become less invasive. Due to the hypofractionated scheme, the physician must pay attention to new dosimetric constraints and new radiologic post-treatment aspects. Although there seems to be a link between BED and local control, new radiobiological models are needed to assess the optimal fractionation and dose scheme. These limitations imply that SBRT should only be conducted by experienced multidisciplinary teams at the time being.

Some SBRT indications, such as lung primary tumors treatments, have become a standard of care for inoperable patients. SBRT seems to be effective in many other indications in curative or palliative intent such as primary liver tumors. Novel indications and strategies are currently emerging, for example prostate cancer treatment or associations of chemotherapy and SBRT.

Currently, SBRT is mainly used when there is no other therapeutic alternative for the patient. This is due to the lack of randomized trials in these settings. However, the results

shown in retrospective studies let us hope to impose SBRT as a new standard of care for many patients in the next few years.

## Conflict of interest

Not declared.

## Financial disclosure

Not declared.

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